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(71) Applicant: CADILA PHARMACEUTICALS LIMITED [IN/IN]; IRM House, Off. CG Road, Navrangpura, Ahmedabad 380 006, Gujarat (IN).

(71) Applicant and
(72) Inventor: KHAMAR, Bakulesh, Mafatlal [IN/IN]; 201 Ashadha, Vasundhara Colony, Gulbai Tekra, Ellisbridge, Ahmedabad 380 006, Gujarat (IN).

(72) Inventor: GUMUDAVELLI, Sridhar, Krishnamurthy; Cadila Pharmaceuticals Limited, IRM House, Off. CG Road, Navrangpura, Ahmedabad 380 006, Gujarat (IN).

(74) Common Representative: KHAMAR, Bakulesh, Mafatlal; 201 Ashadha, Vasundhara Colony, Gulbai Tekra, Ellisbridge, Ahmedabad 380 006, Gujarat (IN).

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/07736 A1

(54) Title: THE PROCESS FOR MANUFACTURING OF CLEAR LIQUID PHARMACEUTICAL COMPOSITION OF AZITHROMYCIN

(57) Abstract: Azithromycin is a macrolide antibiotic used for treating infections. This is available in a solid oral dosage form. It is desirable to have a clear liquid formulaiton also for treating severe infections by intravenous administration of the drug. Currently, it is not possible to manufacture liquid preparation which is ready to use. As it is not soluble in water or other known solvents, for this purpose, it is being marketed as lyophilized preparation which is reconstituted prior to use. According to present invention, it is found that it is soluble in water at pH 5.0. The change in pH can be obtained by adding citric acid in a desired concentration. However, this solution is not stable, and precipitates are seen over the time. According to the present invention, this solution is stabilized by addition of sodium salts like sodium hydroxide, thereby changing its pH from 5.0 to 7.0. The solution so prepared remains clear and is stable for a longer period.

FORM 2

THE PATENTS ACT, 1970

THE COMPLETE SPECIFICATION

(See section 10)

1. THE PROCESS FOR MANUFACTURING OF CLEAR LIQUID PHARMACEUTICAL COMPOSITION OF AZITHROMYCIN

2. Cadila Pharmaceuticals Limited, IRM House, Off C.G. Road, Navrangpura, Ahmedabad- 380009, Gujarat, India, an Indian company.

3. The following specification particularly describes and ascertains the nature of this invention and the manner in which it has to be performed.

FIELD OF INVENTION

The objective of present invention is to manufacture clear liquid pharmaceutical composition of Azithromycin.

BACKGROUND OF THE INVENTION

Azithromycin is the U.S.A.N. (generic name) for 9a-aza-9a-methyl-9-deoxo-9a-homoerythromycin A, a broad spectrum antimicrobial compound derived from erythromycin A. Azithromycin was independently discovered by Bright, U.S. Pat. No. 4,474,768 and Kobrehel et al., U.S. Pat. No. 4,517,359. These patents disclose that azithromycin and certain derivatives thereof possess antibacterial properties and are accordingly useful as antibiotics.

Azithromycin is a macrolide antibiotic used for treating infections. This is available in a solid oral dosage form and for intravenous use as lyophilized powder. It is desirable to have a clear liquid formulation also for treating severe infections by intravenous administration of the drug.

Currently, it is not possible to manufacture liquid preparation which is ready to use. As it is not soluble in water or other known solvents, for this purpose, it is being marketed as lyophilized preparation which is reconstituted prior to use.

REFERENCES:

1. U.S. patent no. 4474768
N-Methyl 11-aza-10-deoxo-10-dihydro-erytromycin A, intermediates therefore.
Bright; Gene M
Pfizer Inc.

2. U.S. patent no. 4517359
11-Methyl-11-aza-4-0-cladinosyl-6-0-desosaminyl-15-ethyl-7,13,14-trihydroxy-3,5,7,9,12,14-hexamethyl-oxacyclopentadecane-2-one and derivatives thereof.
Kobrehel; Gabrijela; Djokic; Slobodan
Sour Pliva farmaceutska, kemijska prehrambena i kozmeticka industrija

SUMMARY OF THE INVENTION

The present invention describes a method for preparing clear liquid pharmaceutical composition of Azithromycin. This is made possible by solubilizing azithromycin in water at pH 4.0 to 6.0 and then adding sodium hydroxide, thereby changing the pH between 6.0 to 7.0.

Azithromycin liquid so prepared as per the invention remains clear and was found to be stable for longer period.

DESCRIPTION OF THE INVENTION

According to the present invention is described a method of preparing clear liquid pharmaceutical composition of Azithromycin.

The objective of the present invention is to provide azithromycin as a liquid preparation which is stable and can be ready to use.

According to present invention it is found that azithromycin is soluble in water at pH between 4.0 to 6.0.

It is also found that azithromycin is soluble in other solvents like polyalcohols which comprises of propylene glycol, glycerine, polyethylene glycol and sorbitol.

However when a solution is prepared using azithromycin at pH between 4.0 to 6.0, it does not remain stable for a long term and develops precipitation. Thus, the pharmaceutical composition prepared is not stable.

It is further observed as per the present invention that when pH is raised further, then azithromycin remains in solution and product is also stable for a longer time.

EXAMPLE 1:

No.	Ingredients	Quantity (per 1000 ml)
1	Azithromycin dihydrate equivalent to Azithromycin anhydrous	1.1 gms
2	Citric acid anhydrous	5.0 gms
3	Sodium hydroxide (50% solution)	2.5
4	Water for Injection Q.S. to	1000 ml

1. Citric acid anhydrous is dissolved in 200 ml Water for injection.
2. The pH of the above solution is adjusted to 4.0 to 6.0 with Sodium hydroxide.
3. Azithromycin is added to this solution and mixed.
4. Now Sodium hydroxide solution is added till clear solution is added, and the pH is between 6.0 to 7.0.
5. The solution is filtered through 0.22 micron membrane and filled in vials.
6. The vials are then sterlized by autoclaving at 120°C with 15 LB pressure for 20 minutes.

EXAMPLE 2:

Solvents which can be used for the preparation of liquid formulation of Azithromycin are:

1. Water
2. Polyalcohol:
   a) Propylene glycol
   b) Polyethylene glycol
   c) glycerine
   d) Sorbitol

The preparation so prepared as per the present invention can be used for administration through oral or parenteral route.

We claim:

1. The process of manufacturing clear liquid pharmaceutical composition of Azithromycin, comprises the steps of:
   a) Adding azithromycin to solvent with appropriate pH.
   b) Mixing of above preparation to obtain clear liquid preparation.

2. The clear liquid preparation of azithromycin as claimed in claim 1 is further stabilized by bringing pH from 5.5 to 7.0.

3. The solvent as claimed in claim 1 is water.

4. The solvent as claimed in claim 1 is a polyalcohol like propylene glycol, glycerine, polyethylene glycol and the like.

5. The solvent as claimed in claim 1 and 4 is selected from propylene glycol, glycerine, polyethylene glycol, sorbitol and the like.

6. The solvent as claimed in claim 1 is made up of single ingredient or a combination of them.

7. The pH as claimed in claim 1 is between 4.0 to 6.0.

8. The process as described in claim 1 and as described in examples 1 and 2.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 01/01313

CLASSIFICATION OF SUBJECT MATTER

IPC[7]: A31K 31/7048, 31/7052, 9/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[7]: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, EPODOC, PAJ,

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0307128 A2 (PFIZER) 15 March 1989 (15.03.89) *example 5.*	1-3,5-7
P,X	EP 1075837 A2 (S.I.F.I. Societa Industria Farmaceutica Italiana S.p.A.) 14 February 2001 (14.02.01) *page 4, lines 21-29; claims 1-6,12.*	1-3,5-7
P,X	WO 00/57866 A2 (INSITE VISION INC.) 5 October 2000 (05.10.00) *abstract; page 10, lines 5-14; page 13, lines 5-22; claim 1.*	1-7

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
„A" document defining the general state of the art which is not considered to be of particular relevance
„E" earlier application or patent but published on or after the international filing date
„L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
„O" document referring to an oral disclosure, use, exhibition or other means
„P" document published prior to the international filing date but later than the priority date claimed
„T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
„X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
„Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
„&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 November 2001 (06.11.2001)	6 December 2001 (06.12.2001)
Name and mailing adress of the ISA/AT Austrian Patent Office Kohlmarkt 8-10; A-1014 Vienna Facsimile No. 1/53424/535	Authorized officer KRENN Telephone No. 1/53424/435

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 01/01313

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 8
because they relate to subject matter not required to be searched by this Authority, namely:

Apart from its reference to the description (which is not allowed according to PCT-Rule 6.2.) claim 8 does not refer to any technical feature.

2. ☒ Claims Nos.: 1
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

According to PCT-Article 6 claims should be (1) clear and concise and (2) supported by the description. Although claim 1 does not correspond to said requirement, the search was carried out restricting the subject matter of claim 1 to the specifications made in claims 2 and 3. Moreover the term "..and the like." was not considered within the search.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/IB 01/01313

Patent document cited in search report			Publication date	Patent family member(s)			Publication date
EP	A2	307128	15-03-1989	AT	E	74508	15-04-1992
EP	A3	307128	04-07-1990	AU	A1	82800/87	17-04-1989
EP	B1	307128	08-04-1992	AU	A1	22061/88	11-05-1989
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				US	A	4963531	16-10-1990
EP	A2	1075837	14-02-2001	IT	A0	991803	09-08-1999
EP	A3	1075837	16-05-2001	JP	A2	01089378	03-04-2001
				US	BA	6277829	21-08-2001
WO	A	0057866		none			